## REMARKS

In the instant Action, Claims 11 and 52-55 are listed as pending, Claims 54 and 55 are listed as withdrawn from consideration, and Claims 11, 52 and 53 are listed as rejected.

Initially, Applicants appreciatively note the following actions of the Examiner in the instant Action:

- The Examiner entered the Amendments and Response submitted on June 25, 2007.
- The Examiner withdrew the objection to Claim 12 for being a substantial duplicate of Claim 11.
- The Examiner withdrew the rejection of Claims 9, 10, 13-15 and 23-29 under 35 U.S.C. §112, first paragraph.
- The Examiner withdrew the double patenting rejection of Claims 9-15 and 23-29 over USP 5,717,062.
- The Examiner withdrew the rejection of Claims 9-15 and 23-29 under 35 U.S.C. §102(b) over Gardella, *et al.* (1996, J. Biol. Chem., 271(33): 19888-19893).
- The Examiner withdrew the rejection of Claim 9 under 35 U.S.C. §102(b) over Neugebauer and Willick (1993, Peptides 1992, C.H. Schneider and A.N. Eberle (eds), ESCOM Science Publishers).
- The Examiner withdrew the rejection of Claim 9 under 35 U.S.C. §102(b) over USP 5,556,940.
- The Examiner withdrew the rejection of Claims 9, 10, 12-15 and 23-29 under 35 U.S.C. §102(e) over USP 5,717,062.

### I. Maintenance of Double Patenting Rejection of Claims 11, 52 and 53 over the '577 Patent

In the instant Action, the Examiner has maintained the rejection of Claims 11, 52 and 53 under the judicially created doctrine of double patenting over Claims 1, 2, 3, 4, 9, 13, 18 and 19 of U.S. Patent No. 5,723,577 (the "'577 Patent").

In the instant Action, the Examiner repeatedly states that the essential point of the rejection is that "the discovery of a previously unappreciated property of a prior art composition [

] does not render the old composition patentably new to the discoverer", citing MPEP §2112, referring to *In re Best*, 562 F.2d 1252, 195 USPQ 430, 433 (CCPA 1997) and *In re Crish*, 393 F.3d 1253, 73 USPQ2d 1364, 1368 (Fed. Cir. 2004).

Whilst Applicants do not disagree with this basic tenet, Applicants submit that this tenet simply is not applicable to the instant Application in view of the fact that, for example, Claim 11 was amended to be directed to but one compound, [Cha$^{7,11}$, des-Met$^{8}$, Nle$^{18}$, Tyr$^{34}$]hPTH(1-34)$NH_2$ (SEQ ID NO:16) which is not encompassed by Claims 1, 2, 3, 4, 9, 13, 18 and 19 of the '577 Patent. Claim 1 of the '577 Patent, in relevant part, is copied below for close examination:

**1. A peptide of the formula:**

$$R_1 \diagdown A_1\text{—Val—}A_3\text{—Glu—}A_5\text{—Gln—}A_7\text{—}A_8\text{—His—} \diagup R_2$$

$$\text{Asn—}A_{11}\text{—}A_{12}\text{—Lys—His—}A_{15}\text{—}$$

$$A_{16}\text{—}A_{17}\text{—}A_{18}\text{—}A_{19}\text{—Arg—}A_{21}\text{—Glu—}A_{23}\text{—}A_{24}\text{—Arg—}$$

$$\text{Lys—}A_{27}\text{—}A_{28}\text{—Gln—}$$

$$A_{30}\text{—}A_{31}\text{—}A_{32}\text{—}A_{33}\text{—}A_{34}\text{—}R_3,$$

wherein

$A_1$ is Ser. Ala. or Dap;
$A_3$ is Ser. Thr. or Aib;
$A_5$ is Ile or Cha;
$A_7$ is Leu. Nle. Cha. β-Nal. Trp. Pal. Phe. or p-X-Phe in which X is OH. a halogen. or $CH_3$;
$A_8$ is Met. Nva. Leu. Val. Ile. Cha. or Nle;
$A_{11}$ is Leu. Nle. Cha. β-Nal. Trp. or Phe;
$A_{12}$ is Gly;
$A_{15}$ is Leu or Cha;
$A_{16}$ is Ser. Asn. Ala. or Aib;
$A_{17}$ is Ser. Thr. or Aib;
$A_{18}$ is Met. Nva. Leu. Val. Ile. Nle. Cha. or Aib;
$A_{19}$ is Glu or Aib;
$A_{21}$ is Val. Cha. or Met;
$A_{23}$ is Trp or Cha;
$A_{24}$ is Leu or Cha;
$A_{27}$ is Lys. Aib. Leu. hArg. Gln. or Cha;
$A_{28}$ is Leu or Cha;
$A_{30}$ is Asp or Lys;
$A_{31}$ is Val. Nle. Cha. or deleted;
$A_{32}$ is His or deleted;
$A_{33}$ is Asn or deleted;
$A_{34}$ is Phe. Tyr. Amp. Aib. or deleted;

It is clear that Claim 1 of the '577 Patent does NOT allow the possibility of $A_8$ being "des-Met",[1] and as such, the Examiner is incorrect in asserting that "[t]he claimed analogues of Patent 5,723,577 are the same as the PTH analogues of the instant Application and would therefore possess the same *inherent* characteristics concerning PTH2 binding affinity and efficacy (Kd and EC50, respectively; see Table I of Patent 5,723,577 for PTH-R binding affinities)." *See* pages 5-6 of the instant Action. If the Examiner decides to maintain this rejection, Applicants respectfully request that the Examiner specifically show how the claimed analogues of the '577 Patent are the ***same*** – and not merely ***similar*** – as the claimed PTH analogues of the instant Application. Applicants respectfully submit that such sameness cannot be established, and as such, the Examiner's essential point of the rejection that "the discovery of a previously unappreciated property of a prior art composition [ ] does not render the old composition patentably new to the discoverer" is simply not applicable in this case.

Moreover, it is respectfully submitted that the Examiner's reference to Table I of the '577 Patent for the PTH/PTHrP (*i.e.*, PTH-*1*) receptor binding affinities is simply irrelevant, because the essential inventive feature of the claimed compounds is that they selectively bind to the PTH-*2* receptor. Please see page 4 of the corresponding International Application No. PCT/US99/09521, published as [WO 99/57139], wherein Applicants state:

> The development of specific ligands which activate the PTH2 receptor but not the PTH/PTHrP receptor, would be highly useful in defining the physiological roles of the PTH2 receptor and its potential involvement in certain pathological states. We have discovered a series of PTH2 receptor-selective PTH analogues which interact selectively with the human PTH2 receptor and are practically devoid of PTH/PTHrP receptor interaction. The compounds of the present invention are not only selective toward a receptor subtype but also signal specifically through the stimulation of $[Ca^{+2}]_i$ transients. Therefore, the compounds of the present invention are receptor subtype and signaling pathway selective.

That is, the essential difference between the claimed compounds of the instant Application and the claimed compounds of the '577 Patent is that, while the former compounds selectively bind to the PTH-2 receptor, the latter compounds – by virtue of the fact that they are not the same compounds as the former compounds – do not necessarily selectively bind to the PTH-2 receptor. By referring to Table I of the '577 Patent, which putatively show the claimed compounds of the

[1] Likewise, Claim 1 of the '574 Patent does NOT allow the possibility of $A_8$ being "D-Nle" nor $A_{18}$ being "des-Met".

'577 Patent's ability to bind to the PTH/PTHrP (PTH-1) receptor, the Examiner's assertion at most amounts to a ***suggestion*** that the structurally ***similar*** – but not the ***same*** as the claimed compounds of the instant Application – compounds of the '577 Patent ***likely*** – but not ***necessarily*** and ***inherently*** – possess the ability to selectively bind to the PTH-***2*** receptor by virtue of their ability to bind to the PTH-***1*** receptor. In fact, in the *previous* Office Action mailed on January 25, 2007, at page 10, the Examiner stated that "since the structures of many of the peptides are ***similar*** in the '577 Patent, it ***might be expected*** that some of those compounds would ***likewise*** be "selective" for the PTH2 receptor as well." (emphasis added).

However, the PTH-***1*** receptor is NOT the SAME as the PTH-***2*** receptor.[2] It is not an inherent property, therefore, of compounds that bind to the PTH-***1*** receptor to selectively bind to the PTH-***2*** receptor.[3] *Cf.* MPEP §2112, "The fact that a certain result or characteristic ***may*** occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. (emphasis original), citing *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). Also, "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

Furthermore, "[a]n invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites

[2] Please see pages 3-4 of the corresponding International Application No. PCT/US99/09521, published as [WO 99/57139], for the detailed description of the distinction between the PTH-1 receptor and the PTH-2 receptor.

[3] In fact, in the *previous* Office Action mailed on January 25, 2007, at pages 12-13, the Examiner stated that "[i]t is interesting to note ... that the prior reference discloses a structurally wide variety of peptides with wide ranges of binding characteristics, not only encompassing the applicants' claimed invention but demonstrating that ***minor changes in the sequences of "PTH" peptides produce significant changes in function***." (emphasis added).

further experimentation to find the species.). Applying this case law precedent to the instant Application, Claim 1 of the '577 Patent, which discloses a broad genus, does not inherently disclose the claimed species of the instant Application within that broad category, because, as discussed above, it does not even encompass the claimed compounds of the instant Application; and as such, it merely invites further experimentation to find the species. This conclusion, which is dictated by the case law precedent, is in sharp contrast to the Examiner's ***suggestion*** that the structurally ***similar*** – but not the ***same*** as the claimed compounds of the instant Application – compounds of the '577 Patent ***likely*** – but not ***necessarily*** and ***inherently*** – possess the ability to selectively bind to the PTH-***2*** receptor by virtue of their ability to bind to the PTH-***1*** receptor.

Even so, nowhere in Claims 1, 2, 3, 4, 9, 13, 18 and 19 of the '577 Patent is it suggested that the specific claimed compounds of the instant Application possess the ability to selectively bind to the PTH-2 receptor and to significantly stimulate the cytosolic calcium secondary messenger pathway. *See, e.g., Eli Lilly & Co. v. Barr Industries, Inc.*, 222 F.3d 973, 986, 55 USPQ2d 1609, 1918 (Fed. Cir. 2000) ("a species claim is not necessarily obvious in light of a prior art disclosure of a genus."); *In re Deuel*, 51 F.3d 1552, 1558-59, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995) ("A prior art disclosure of the amino acid sequence of a protein does not necessarily render particular DNA molecules encoding the protein obvious because the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences coding for the protein. No particular one of these DNAs can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared."); *In re Baird*, 16 F.3d 380, 383, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("A disclosure of millions of compounds does not render obvious a claim to three compounds").

In response to the Examiner's concerns that "no data was generated that might illuminate the differences between and among the 'selective' compounds", *see* page 10 of the *previous* Office Action mailed on January 25, 2007, Applicants previously submitted the Chorev Declaration to the effect that the three compounds of Claim 52 selectively bind to the PTH-2 receptor and are shown to significantly stimulate the cytosolic calcium secondary messenger pathway. It is submitted that the experimental data on the three compounds of Claim 52 in the Chorev Declaration are sufficient to provide experimental support for the claimed compounds, to the effect that the specific claimed compounds of the instant Application show unexpectedly

superior results with respect to their ability to selectively bind to the PTH-2 receptor and significantly stimulate the cytosolic calcium secondary messenger pathway, in such a manner heretofore unappreciated by the teaching of the '577 Patent.

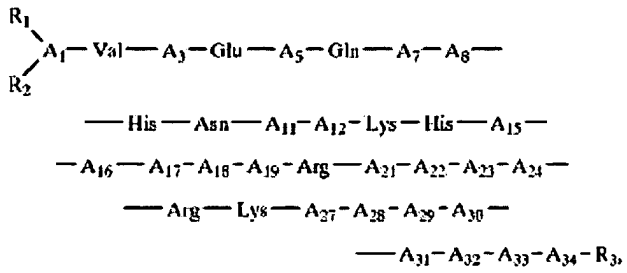
Accordingly, reconsideration and withdrawal of the rejection of Claims 11, 52 and 53 under the judicially created doctrine of double patenting over Claims 1, 2, 3, 4, 9, 13, 18 and 19 of the '577 Patent is respectfully requested. Furthermore, should the Examiner determine that Claims 11, 52 and 53 are allowable, rejoinder of claims 54-55 is respectfully requested.

## II. Maintenance of Double Patenting Rejection of Claims 11, 52 and 53 over the '574 Patent

In the instant Action, the Examiner has maintained the rejection of Claims 11, 52 and 53 under the judicially created doctrine of double patenting over Claims 1-4 of U.S. Patent No. 5,955,574 (the "'574 Patent"), for reasons of record. Specifically, at page 7 of the instant Action, the Examiner states that Claims 1-4 of the '574 Patent "specifically embrace the compounds listed in instant Claims 11, 52 and 53. Applicants again categorically traverse this factual assertion. That is, the '574 Patent does not "specifically embrace the compounds listed in instant Claims 11, 52 and 53." Claim 1 of the '574 Patent, in relevant part, is copied below:

[*Remainder of the page intentionally left blank*]

1. A peptide of the formula:



wherein

$A_1$ is Ser, Ala, or Dap;

$A_3$ is Ser, Thr, or Aib;

$A_5$ is Leu, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe or p-X-Phe, in which X is OH, a halogen, or $CH_3$;

$A_7$ is Leu, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, or p-X-Phe in which X is OH, a halogen, or $CH_3$;

$A_8$ is Met, Nva, Leu, Val, Ile, Cha, Acc, or Nle;

$A_{11}$ is Leu, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe or p-X-Phe in which X is OH, a halogen, or $CH_3$;

$A_{12}$ is Gly, Acc, or Aib;

$A_{15}$ is Leu, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, or p-X-Phe in which X is OH, a halogen, or $CH_3$;

$A_{16}$ is Ser, Asn, Ala, or Aib;

$A_{17}$ is Ser, Thr, or Aib;

$A_{18}$ is Met, Nva, Leu, Val, Ile, Nle, Acc, Cha, or Aib;

$A_{19}$ is Glu or Aib;

$A_{21}$ is Val, Acc, Cha, or Met;

$A_{22}$ is Acc or Glu;

$A_{23}$ is Trp, Acc, or Cha;

$A_{24}$ is Leu, Acc, or Cha;

$A_{27}$ is Lys, Aib, Leu, hArg, Gln, Acc, or Cha;

$A_{28}$ is Leu, Acc, or Cha;

$A_{29}$ is Glu, Acc, or Aib;

$A_{30}$ is Asp or Lys;

$A_{31}$ is Val, Leu, Nle, Acc, Cha, or deleted;

It is clear that Claim 1 of the '574 Patent does NOT allow the possibility of $A_8$ being "des-Met", and as such, the Examiner is incorrect in asserting that Claims 1-4 of the '574 Patent "specifically embrace the compounds listed in instant Claims 11, 52 and 53." Likewise, Claim 1 of the '574 Patent does NOT allow the possibility of $A_8$ being "D-Nle" nor $A_{18}$ being "des-Met". If the Examiner decides to maintain this rejection, Applicants respectfully request that the Examiner show how the claimed analogues of the '574 Patent are the ***same*** as the PTH analogues of the instant Application. Applicants respectfully assert that such sameness cannot be

established, and as such, the Examiner's essential point of the rejection that "the discovery of a previously unappreciated property of a prior art composition [ ] does not render the old composition patentably new to the discoverer" is simply not applicable in this case.

Accordingly, absent a specific showing that the '574 Patent is a novelty-destroying prior art reference with respect to the single PTH analogue compound of Claim 11, or the three PTH analogue compounds of Claim 52, Applicants respectfully request reconsideration and withdrawal of this rejection. Furthermore, should the Examiner determine that Claims 11, 52 and 53 are allowable, rejoinder of claims 54-55 is respectfully requested.

## III. Maintenance of Rejection of Claims 11, 52 and 53 under 35 U.S.C. §102(e)

In the instant Action, the Examiner has maintained the rejection of Claims 11, 52 and 53 under 35 U.S.C. §102(e) as being anticipated by the '574 Patent. As discussed above in connection with the Examiner's maintenance of the doctrine of double patenting rejection over Claims 1-4 of '574 Patent, absent a specific showing that the '574 Patent is a novelty-destroying prior art reference with respect to the single PTH analogue compound of Claim 11, or the three PTH analogue compounds of Claim 52, Applicants respectfully request reconsideration and withdrawal of this rejection.

## CONCLUSION

Reconsideration of the instant Action, entry of the requested amendments and of the new claims as set forth herein, grant of request for rejoinder and allowance of the all pending and withdrawn claims are respectfully requested.

Prompt and favorable action is solicited.

Examiner Wegert is invited to telephone Applicants' attorney at (508) 478-0144 to facilitate prosecution of this application.

With the exception of the fee for the aforementioned extension, Applicants are unaware of any additional fees due and owing with respect to this filing, however, if the Applicants' understanding is incorrect, the Commission is authorized to apply any charges and/or credits to Deposit Account No. 50-0590 referencing attorney docket number 073/US/PCT/US.

Respectfully submitted,

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